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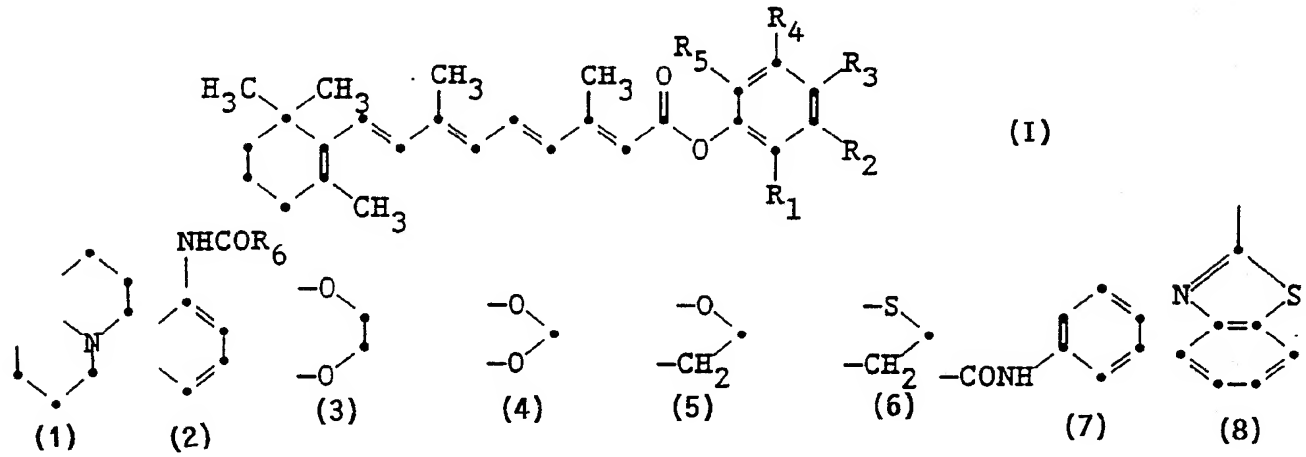
(54) Title: SKIN COMPOSITION TO REPAIR THE EFFFECTS OF PHOTOAGING



(57) Abstract

The effects of photoaging or sun damage of skin including loss of collagen fibers and deterioration of small blood vessels in the dermis of the skin are repaired by applying topically to the epidermis effective amounts of a compound having structure (I), wherein R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, OR_6, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$, R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a (1) moiety or together with R_2 forms a (2) moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a (3) or (4) or (5) or (6) moiety, or R_1 is independently selected from the group consisting of (7), (8) moiety, R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof, to an area of the skin in an amount sufficient to repair the effects of elastosis in the skin. Lines and wrinkles due to aging are reduced and prevented.

* See back of page

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SKIN COMPOSITION TO REPAIR THE EFFECTS OF PHOTOAGING

Cross-Reference to Related Applications

This application is a Continuation-In-Part of copending U.S. Application Serial No. 384,949 filed on July 25, 1989.

Field of the Invention

This invention relates to a method of repairing the effects of aging of the skin, particularly human facial skin, by topical application of specific polyene compositions.

Background of the Invention

Excessive exposure of human skin to sunlight causes damage, resulting in a number of gross cutaneous changes. These include wrinkling, leatheriness, yellowing, looseness, roughness, dryness, mottling (pigment spots) and benign and malignant skin tumors. A person exhibiting these signs looks prematurely aged. Photoaging is most prominent in light skinned persons who brown easily and tan poorly. The effects of sunlight are cumulative. As a result, this sunlight-induced skin damage has been referred to as photoaging.

The majority of signs of photoaging can be prevented by judicious use of topically applied sunscreen agents. It is important to use sunscreens early in life, for example, as soon as a child begins to spend a significant amount of time outdoors.

Many persons will neglect to use sunscreens, and worse, some will intentionally overexpose themselves to natural or artificial sunlight to benefit from cosmetic attributes of tanned skin. Later in life, they will seek medical care in the hope of alleviating the skin damage, for instance, by undergoing cosmetic surgery.

A pharmaceutical composition that can promote the repair of photoaged skin is an alternative treatment to patients who neglect to use sunscreens and do not prefer cosmetic surgery. Topically applied all-trans retinoic acid is reported to improve the appearance of photoaged skin in open and double-blind studies. The beneficial changes were clinically significant to the investigators and the patients. These included effacement of fine wrinkles, reduced skin roughness, increased pinkening of the skin and lightening of pigmented sessions (lentigines, solar-induced freckles).

In the double-blind study, it was reported that 92 percent of patients experienced a dermatitis characterized by patchy erythema, localized swelling, xerosis, and mild scaling. Eleven of the patients needed potent topical steroids to alleviate the dermatitis. Three patients withdrew from the study because of the severity of retinoid-induced dermatitis.

It has been sought to provide a method for the treatment of photoaged skin, but without the adverse effects of dermatitis as noted with all-trans retinoic acid treatment.

The use of 13-cis-retinoic acid as a treatment for the adverse effects of elastosis is described in Australian Patent AU-A-83027187 by Hoffman-La Roche and European Patent Application Publication 0253393.

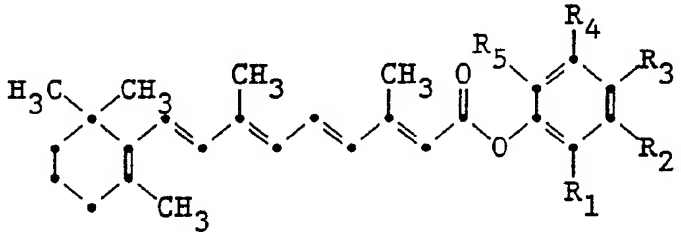
In U.S. Patent 4,595,696 certain polyenes are described as being useful in treating inflammatory or allergic conditions. These conditions, of course are far afield of photoaging and materials useful for the treatment of inflammatory conditions are not expected to be useful in the treatment of photoaging and vice versa.

In U.S. Patent 4,603,146 it is disclosed that all-trans retinoic acid (retin A) is useful in the treatment of photoaging. However, this treatment also results in great irritation to the skin, which severely limits its usefulness.

Summary of the Invention

The present invention relates to the use of specific polyenes in repairing the aging changes of exposed areas of the skin, especially the face. These polyenes retard and reverse the loss of collagen fibers and deterioration of small blood vessels without substantially adversely affecting the patient.

The method of the invention comprises the repairing of sun-damaged skin comprising topically administering a compound having the structure:

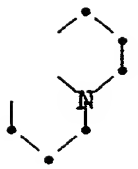


wherein

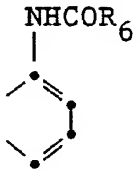
R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, OR_6, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1

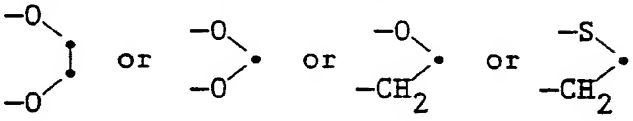
forms a:



moiety or together with R_2 forms a

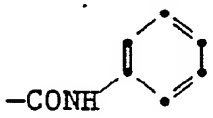


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



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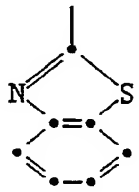


moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof, to an area of the skin in an amount sufficient to repair the effects of elastosis in the

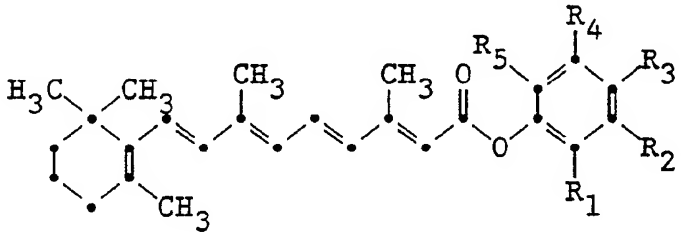
skin. Lines and wrinkles due to aging are reduced and prevented.

The polyenes may be applied to the skin in any non-toxic, dermatologically acceptable vehicle, preferably a non-volatile emollient or lubricating vehicle in varied concentrations which is more fully described hereinbelow.

Detailed Description of the Preferred Emobidments

The treatment of skin with the polyenes of the present invention moderate and retard the aging changes in the skin to both the dermis and the epidermis. As age and exposure to sunlight increases, the skin's cells divide at a slower rate. The thickness of the epidermis decreases and the horny layer which protects against water loss sheds cells in large groups, resulting in rough, dry and scaling skin. The cells which make up the fiber of the dermis become smaller with increasing age with a loss of collagen fibers. The degradation of these fibers contributes to wrinkling and loss of elasticity.

The polyene compounds useful in the present invention have the structure:

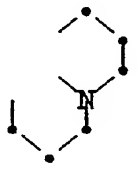


wherein

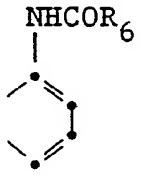
R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, OR_6, straight or branched alkyl of 1 to 10 carbon atoms, for which examples are provided hereinbelow, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$,

$CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

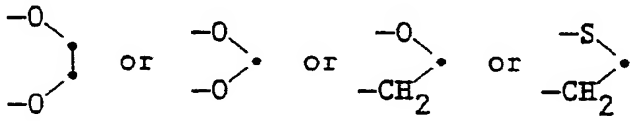
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

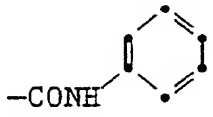


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



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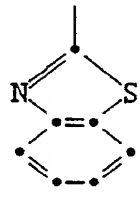


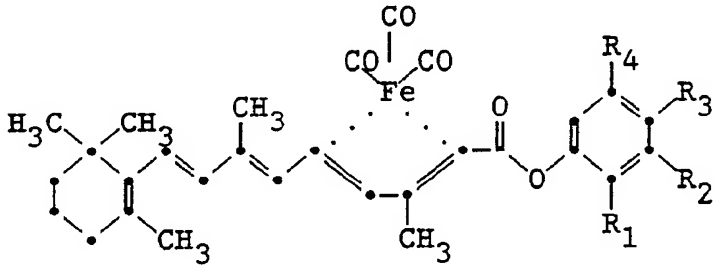
moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms,

for which examples are provided hereinbelow, and aryl containing from 6 to 10 carbon atoms and hydrogen, for which examples are provided hereinbelow, and

R_9 is alkylene of 1 to 6 carbon atoms, such as methylene, propylene, butylene, trimethylene, etc.

and iron carbonyl complexes thereof such as

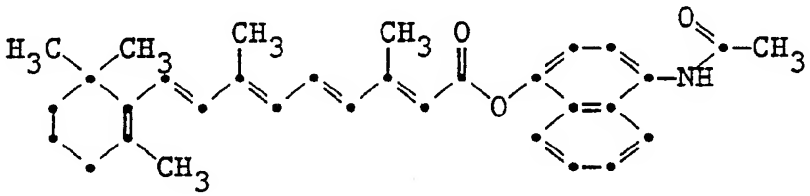


For the purposes of this invention, examples of alkyl of 1 to 10 carbon atoms are methyl, butyl, pentyl, octyl, ethyl, tertiary-butyl, benzyl, isopropyl, chloroethyl, chloropropyl, hydroxypropyl, carboxyethyl, carboxymethyl, phenynyl, cyanoethyl, and 2-ethylhexyl and aryl of 6 to 10 carbon atoms are exemplified by phenyl and napthyl.

The method of preparing these polyenes is well known and is generally described in U.S. Patent 4,595,696(incorporated herein by reference). Generally, the compounds are formed by reaction of polyene acids with acetic anhydride, boron trifluoride, oxalkylene chloride, phosphorous trichloride or thionyl chloride and then further treated with phenolic compounds.

Useful polyenes within the scope of the present invention include those with the following structures:

I.



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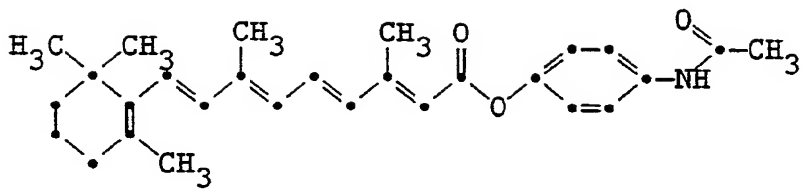

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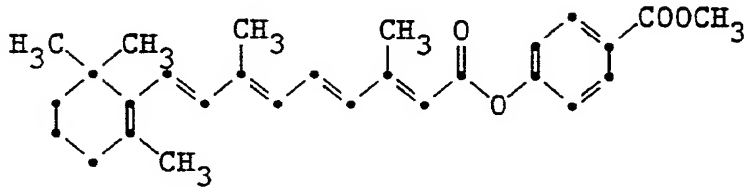

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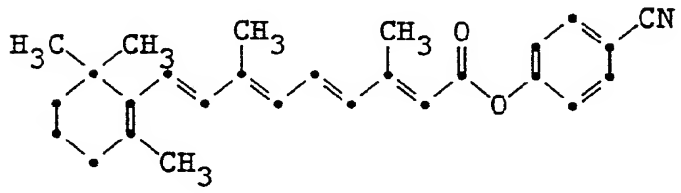

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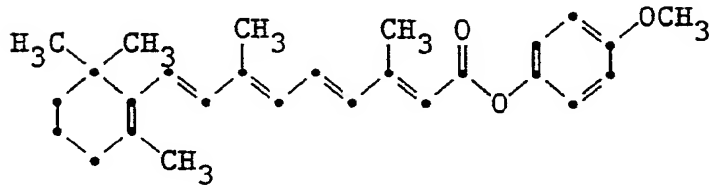

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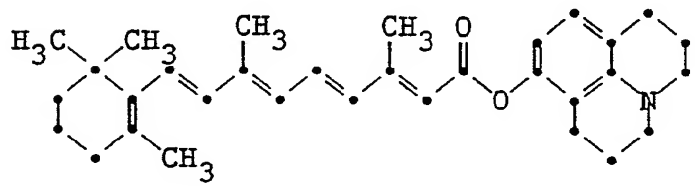

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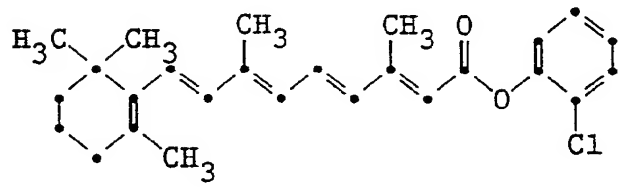

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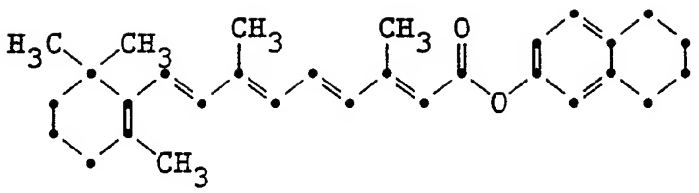

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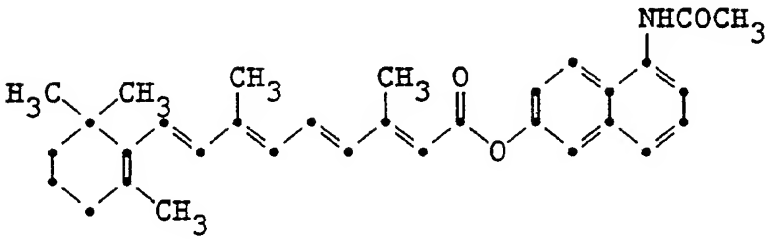

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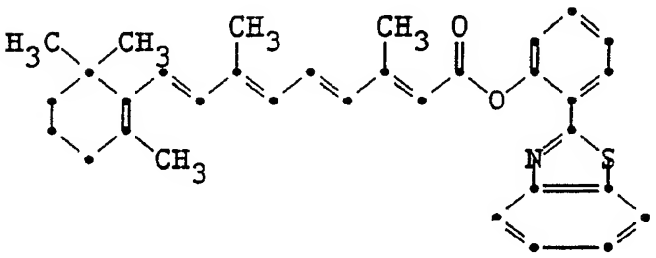

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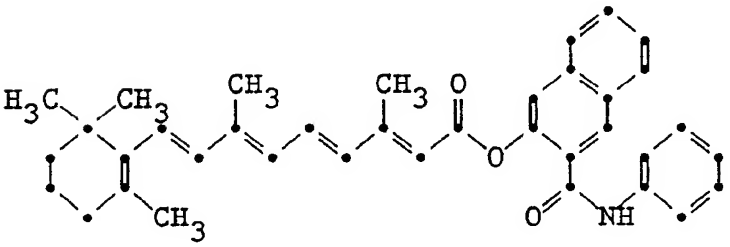

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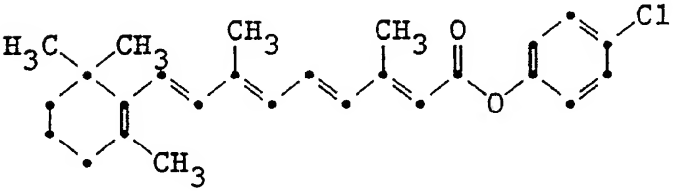

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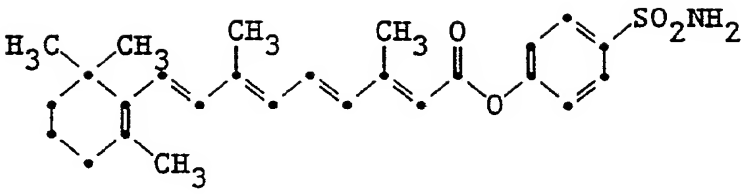

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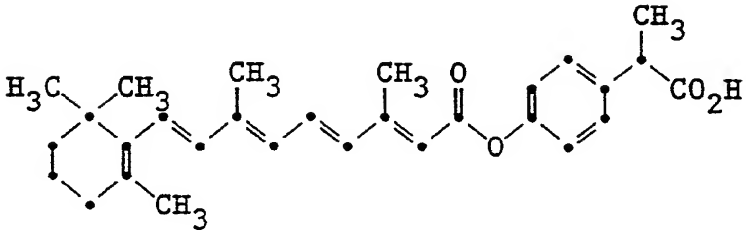

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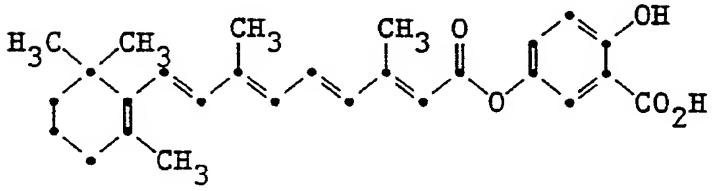

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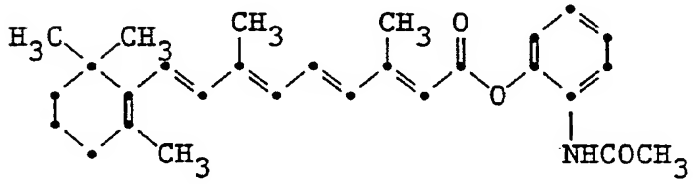

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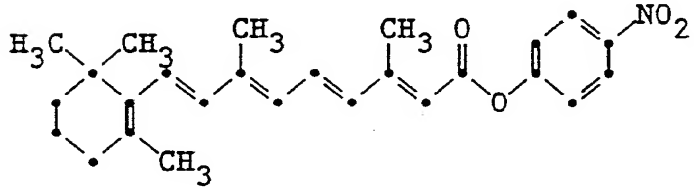

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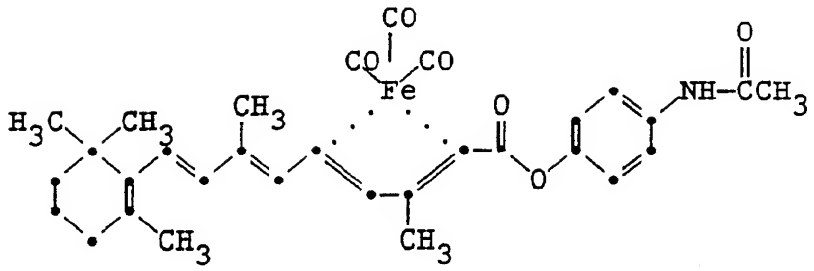

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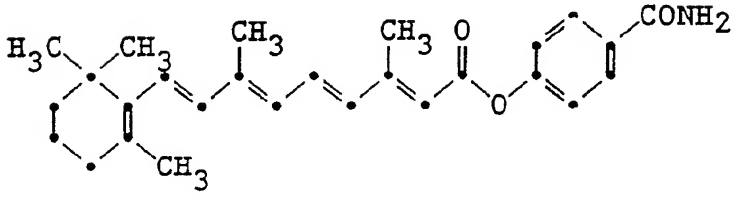

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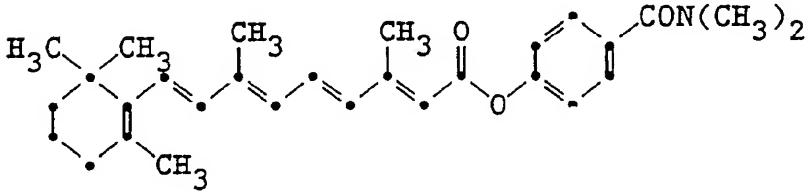
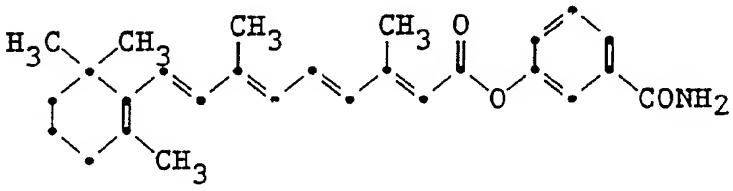


XXI.



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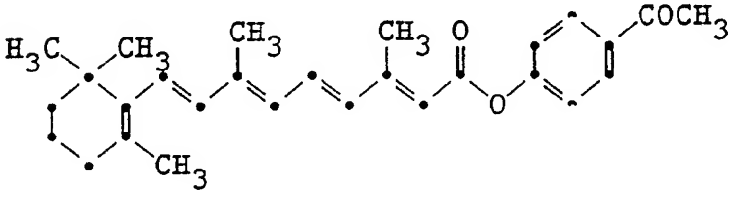

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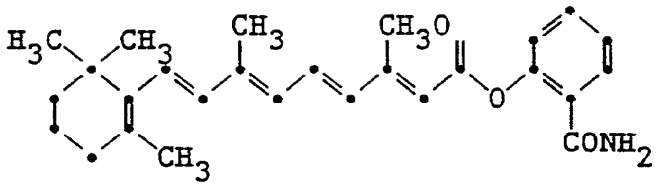

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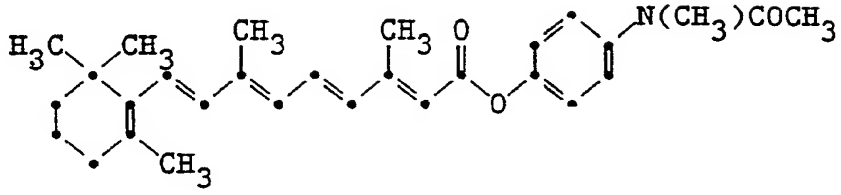

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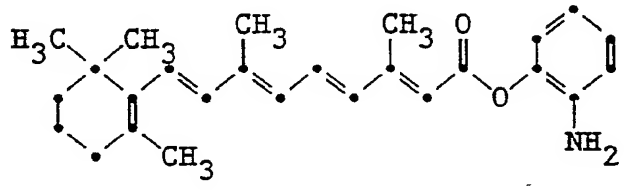

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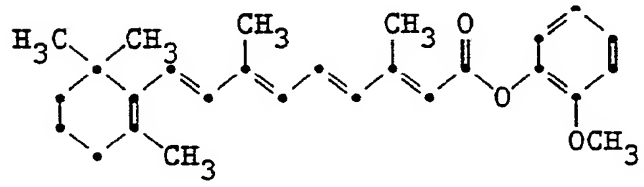

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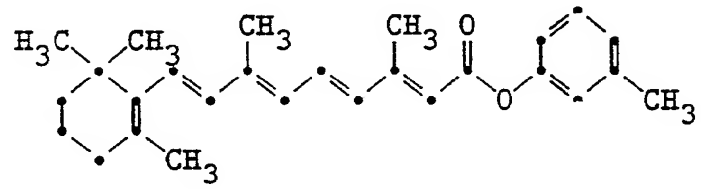

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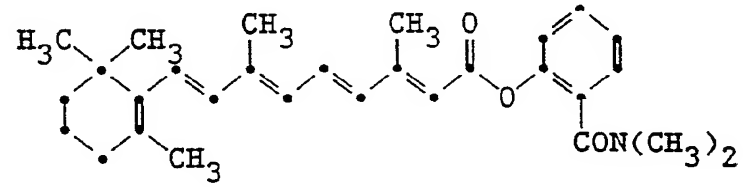

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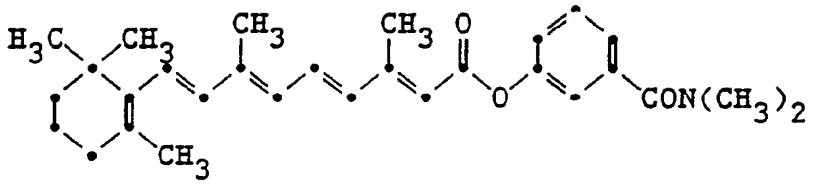

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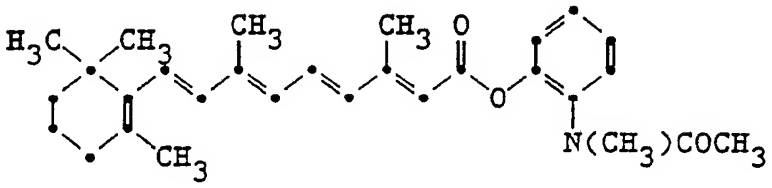

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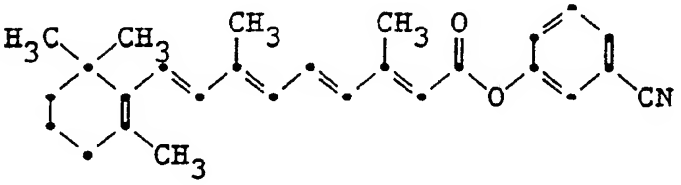

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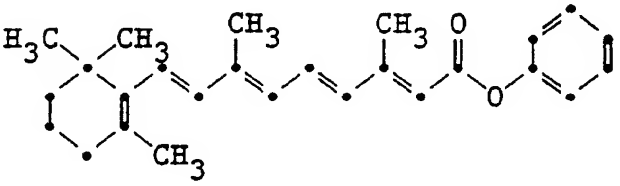

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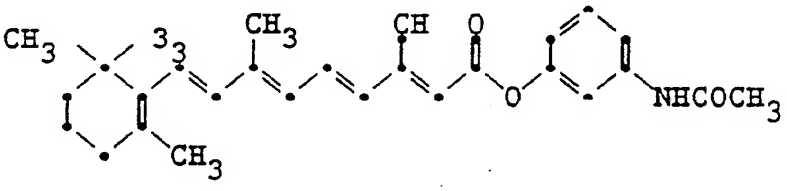

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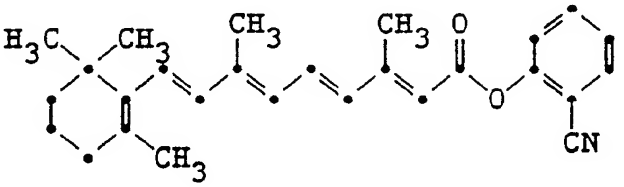

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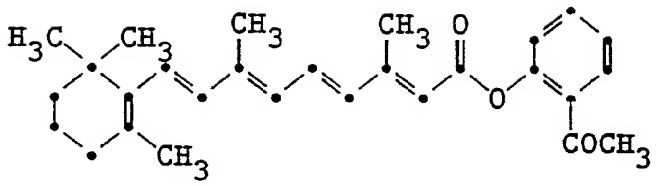

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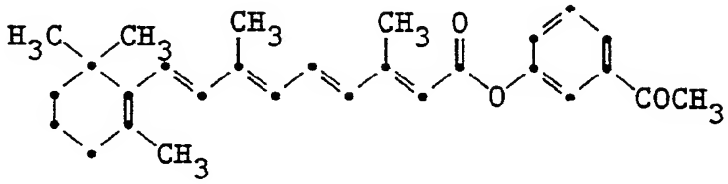

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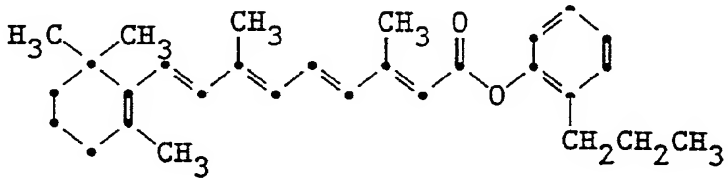

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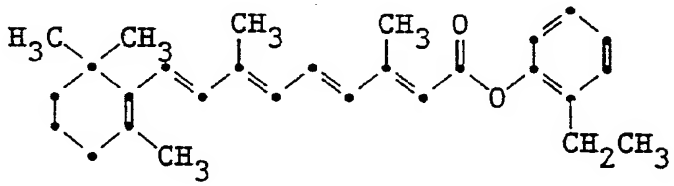

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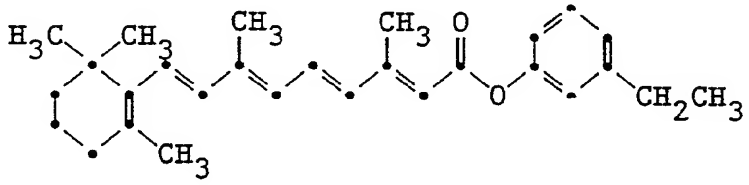

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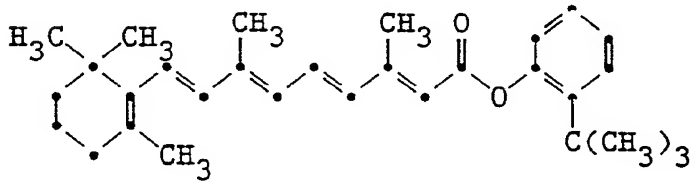

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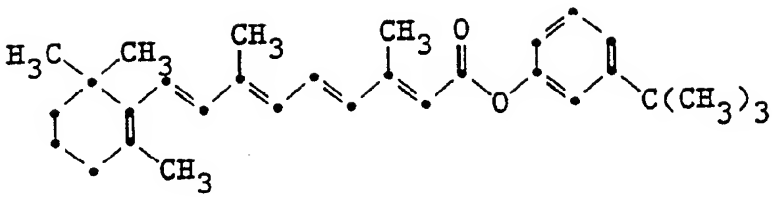

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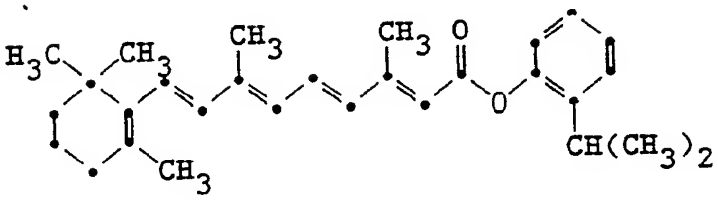

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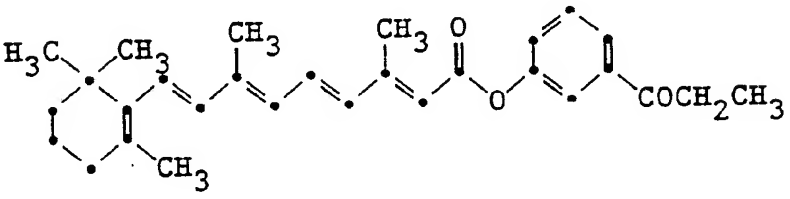

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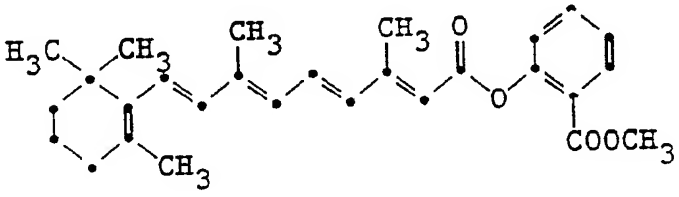

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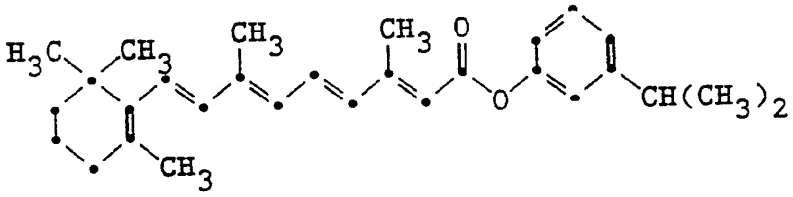

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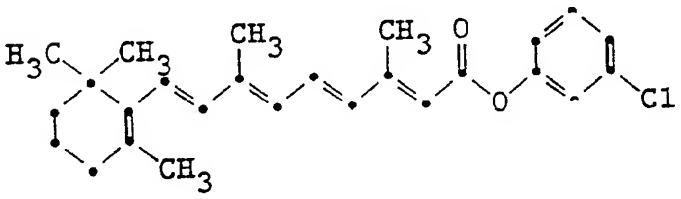

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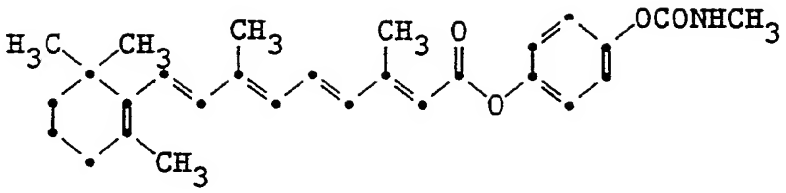

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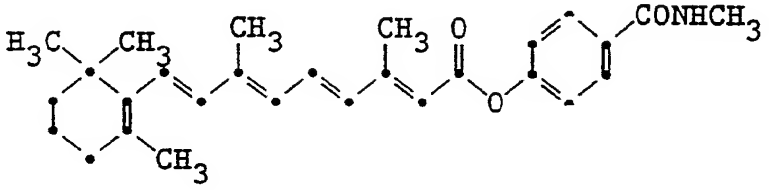

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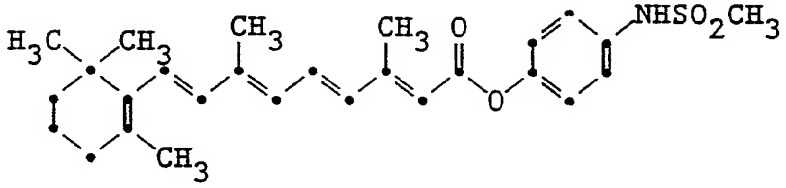

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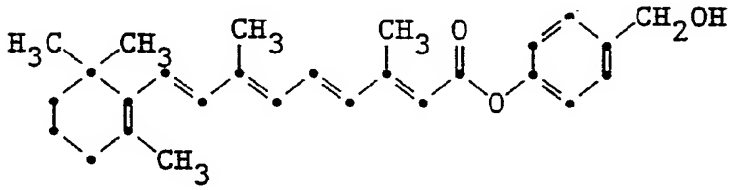

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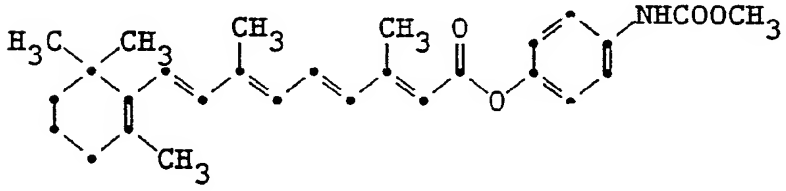

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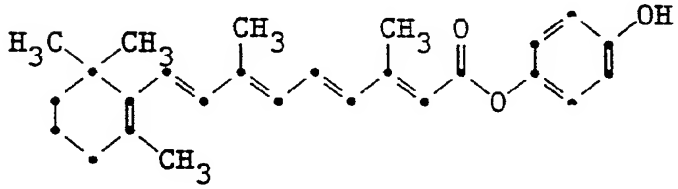


The therapeutic agents of this invention may be administered alone or in combination with pharmaceutically-acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk, sugar, certain of clay and so forth. They may be administered orally in the form of solutions which may contain coloring or flavoring agents. When applied topically for treatment of photoaging, they may be provided in the form of dusting powders, aerosol sprays, ointments, aqueous compositions including solutions and suspensions, cream lotions and the like. In this regard, any of the commonly employed extending agents can be used depending on the nature of the product as is well-known in the art.

The physician will determine the dosage of the present theraputic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached.

The polyenes which are formulated in moisturi- zing bases such as creams or ointments are usually provided in low concentrations. For example, Compound I may be used in concentrations of about 0.001 percent to 10 percent and preferably about 0.01 percent to 5 percent by weight of the base.

Other non-toxic, dermatologically acceptable vehicles or carriers in which the polyenes are stable will be evident to those of ordinary skill in the art. In general, emollient or lubricating vehicles, such as oleaginous substances, which help hydrate the skin are preferred. As used herein, the term "emollient" will be understood to refer to the non-irritating character of the composition as a whole. That is, the nature of the vehicle and amount of polyene therein should be selected so as to provide a sub-irritating dose for topical application. Volatile vehicles which dry or otherwise harm the skin, such as alcohol and acetone, should be avoided.

An ointment base (without water) is preferred in the winter and in subjects with very dry skin. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions, such as Eucerin (Beiersdorf).

In warm weather and often for younger persons, oil in water emulsion (cream) bases, are preferred. Examples of suitable cream bases are Nivea Cream (Beiersdorf), cold cream (USP), Purpose Cream (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm (Warner-Lambert).

The length of treatment of human skin can vary. Usually, there is little point in beginning the treatments of the present invention until young adult life or, more typically, in middle age, when the effects of aging begin to appear. The particular program of maintenance therapy according to the present invention will vary depending upon the individual and conditions being treated. Generally, depending upon the age and state of the skin when treatments begin, it has been found that once a day

applications of polyenes for up to two months may be necessary to reduce and control the effects of aging which have already occurred. Once a stabilized skin control has been obtained, the frequency of application of the polyenes may be reduced, for example to two or three times a week, and in some cases only once a week for the rest of the person's life. That is, once the aging process has been controlled, a maintenance dose on the order of two applications per week is generally sufficient to maintain that state.

The topical compositions of this invention can, if desired, contain suitable sunscreen agents. Any conventional sunscreen agent can be utilized in formulating the polyenes formulations which can be utilized in accordance with this invention.

These topical compositions can contain any of the conventional excipients and additives commonly used in preparing topical compositions. Among the conventional additives or excipients which can be utilized in preparing these cosmetic compositions in accordance with this invention are preservatives, thickeners, perfumes and the like. In addition, the conventional antioxidants, such as butylated hydroxyanisoles (BHA), ascorbyl palmitate, propyl gallate, citric acid butylated hydroxy toluene (BHT), ethoxyquin and the like can be incorporated into these compositions. These topical compositions can contain conventional acceptable carriers for topical applications which are generally utilized in these compositions. These compositions may contain thickening agents, humectants, emulsifying agents and viscosity stabilizers, such as those generally utilized. In addition, these compositions can contain flavoring agents, colorants, and perfume which are conventional in preparing cosmetic compositions.

This invention is further illustrated by the following examples, which are illustrative only.

Example

A. Efficacy Tests

Compound II was tested for its effect on the differentiation of epidermis and dermis in hairless mice and directly compared to all-trans retinoic acid.

In the first test used, polyene compounds related to vitamin A, including all-trans retinoic acid, are highly effective in reducing the size of horn-filled utricles in hairless rhino mouse skin. The number of interutricular epidermal cells layers increases, concomitantly, as the size of the utricles diminish. Increased numbers of epidermal cell layers are also prominent in human photoaged skin treated with all-trans retinoic acid.

Hairless rhino mice ($hr^{rh}hr^{rh}$) from Temple University Skin and Cancer Hospital were treated with 0.05 ml of Compound II, all-trans retinoic acid or the ethanol:acetone (1:1) vehicle on the dorsolateral skin once daily on five consecutive days, for four weeks. Mice were sacrificed by CO_2 on the third day after the last treatments. A 7/8" punch biopsy of skin was removed and bisected in half. One of the halves was placed in 0.5 percent acetic acid overnight at 4°C so that horizontal epidermal sheets could be removed from each biopsy. The following day, epidermal sheets were removed from the dermis by peeling with a metal spatula. These sheets were fixed in formalin, dehydrated with ethanol, and kept in xylene. The other half of the biopsy was placed in 10 percent buffered formalin and processed into hematoxylin and eosin (H&E)-stained vertical sections.

To assess utricle diameter, each epidermal sheet was placed on a glass slide in a few drops of xylene. The diameter of 40 utricles was measured with an image analyzer. The epidermal thickness of the H&E-stained sections was measured on 15 inter-utricular areas of each section with an image analyzer.

Table 1

Dose-Related Activity of Compound II and All-Trans Retinoic Acid on Rhino Mouse Skin Utricle Diameter

Treatment	Percent Concentration, w/v	Mean Diameter µm± S.D.*	Percent Reduction Vs. Vehicle
Vehicle		138 ± 16	0
Compound II	0.5	58 ± 9	58
	0.1	62 ± 10	55
	0.01	73 ± 10	47
	0.001	74 ± 14	46
	0.0001	110 ± 18	20
All-Trans Retinoic Acid	0.1	54 ± 8	61
	0.01	62 ± 9	55
	0.001	70 ± 10	49
	0.0001	95 ± 16	31

* 5 mice per group.

As seen in Table 1, Compound II has marked activity over a wide concentration range, identical to all-trans retinoic acid.

The interutricular epidermal thickness results are shown in Table 2 (on skin samples from the same rhino mice that have their data in Table 1).

Table 2

Dose-Related Activity of Compound II and All-Trans Retinoic Acid on Rhino Mouse Skin Epidermal Thickness

Treatment	Percent Concentration, w/v	Epidermal Thickness µm± S.D.*	Percent Control Vs. Vehicle
Part I			
Compound II	0.5	55.4 ± 8.9	236
	0.1	55.0 ± 8.4	234
	0.01	48.2 ± 3.3	205
	0.001	43.7 ± 6.4	186
	0.0001	35.7 ± 2.5	152
All-Trans Retinoic Acid	0.1	62.2 ± 7.0	265
	0.01	47.7 ± 1.3	203
	0.001	37.6 ± 7.7	160
	0.0001	37.6 ± 6.2	160

*5 mice per group

Compound II was as effective as all-trans retinoic acid in increasing the interutricular epidermal thickness of rhino mice. This increase in epidermal thickness was due to an increase in the number of epidermal cell layers.

Polyene compounds are also evaluated for their effects on epidermal differentiation when they are applied to a non-wrinkled strain of hairless mice (hrhr). These mice have fewer horn-filled utricles in their skin compared to rhino mice. A variety of polyene compounds induce an increase in the number of epidermal cell layers when a compound is applied once to dorsal skin.

Hairless mice, obtained from Jackson Labs, had their dorsolateral skin treated twice, on Days 0 and 1, with 0.05 ml of Compound II, all-trans retinoic acid, or ethanol vehicle. At the peak of the epidermal hyperplasia, on Day 4, the mice were sacrificed by CO_2 and a 7/8" punch biopsy from the treated skin was removed and placed into 10 percent buffered formalin. H&E-stained vertical sections were prepared and the epidermal thickness in the interfollicular areas was measured with an image analyzer.

The results are shown in Table 3.

Table 3

Epidermal Hyperplasis in Hairless Mouse Skin Induced by Compound II and All-Trans Retinoic Acid

Treatment	Percent Concentration, w/v	Epidermal Thickness μm± S.D.*	Percent Control Vs. Vehicle
Vehicle		22.2 ± 3.4	100
Compound II	0.1	56.9 ± 2.6	255
	0.01	53.4 ± 3.0	239
	0.001	37.6 ± 6.1	169
All-Trans Retinoic Acid	0.1	49.3 ± 4.2	221
	0.01	38.9 ± 3.8	174
	0.001	33.3 ± 5.3	149

* 5 mice per group.

At all three concentrations, Compound II caused the same degree of epidermal hyperplasia as the three equivalent concentrations of all-trans retinoic acid.

All-trans retinoic acid is known to affect the differentiation of cells in the dermis of hairless mouse skin, most effectively in the skin of mice that have been damaged by UV radiation. The formation of a new zone of connective tissue is accelerated in photoaged hairless mouse skin by topical treatment with all-trans retinoic acid. This is due to an increased number of fibroblasts and an increase in their metabolic activity. As a result, new collagen bundles and elastic fibers are formed, which leads to a compression of the old, abnormal elastic fibers by the newly created dermal matrix.

Female hairless mice (Skh-HR1), six to eight weeks old, obtained from Temple University Skin and Cancer Hospital, had their dorsal skin irradiated with ultraviolet B (UVB) radiation on Monday, Wednesday and Friday each week for ten weeks, using a bank of eight Westinghouse FS-40 sunlamps placed 16 cm above the back of the mice. During the first three weeks, the radiation dose per day was progressively increased from one minimal erythemal dose (MED) to four MED's. The 4-MED dose per day was then continued for the last seven weeks.

At the end of ten weeks, irradiation was stopped and starting at week eleven, treatment with a 0.05 ml of ethanol vehicle, all-trans retinoic acid, or Compound II was given to the dorsal skin once daily for five consecutive days for ten weeks.

At the end of treatment, mice were sacrificed by cervical dislocation and dorsal skin was removed and placed in 10 percent buffered formalin. Parafin-embedded sections were cut at 10 μm thickness and stained with Luna's aldehyde fuchsin for elastic fibers. The dermal repair zone was measured microscopically and is defined as the area from the epidermal-dermal border to the top of the compressed elastotic material.

The results in Table 4 show that Compound II was as effective as all-trans retinoic acid in causing increased repair of the connective tissue zone.

Table 4

The Depth of the Dermal Repair Zone
Induced in Photoaged Hairless Mouse Skin
by Representative Compounds of

Treatment	Dermal Repair Zone Depth, µm*	Percent Control Vs. Vehicle
Part I		
Untreated	48.1 ± 6.9	109
Vehicle	44.0 ± 21.4	100
Compound II, 0.1 percent	98.4 ± 14.4	224
All-Trans Retinoic Acid, 0.05 percent	110.6 + 21.8	251-277
* 12 mice per group.		
Part II		
Compound XIII, 0.1 percent	101.3	291
Compound IX, 0.1 percent	98.4	282
Compound V, 0.1 percent	90.72	260
All-Trans Retinoic Acid, 0.01 percent	96.44	277
Vehicle	34.79	
Part III		
Compound X, 0.1 percent	82.33	223
Compound XII, 0.1 percent	77.74	210
Compound XV, 0.1 percent	84.68	229
All-Trans Retinoic Acid, 0.1 percent	97.50	264
Vehicle	36.88	

Part IV

Compound XXII	93.71	414
All Trans-Retinoic Acid, 0.1 percent	96.16	425
Vehicle 0.1 percent	22.6	

B. Toxicity Tests

A rabbit model of skin irritation was used to assess the dermatitis produced by treatment with Compound II and all-trans retinoic acid. The rabbit is commonly used as a skin irritation model for predicting the potential local irritation of topically applied materials.

New Zealand albino rabbits, from Beckens Farms, Sanborn, N.Y., were clipped closely at four sites on the back with an electric hair clipper to give 4 cm X 4 cm square sites. Each rabbit received 0.2 ml of Compound II and all-trans retinoic acid, once daily for fourteen consecutive days. Each day, the degree of erythema, scaling and edema was assessed visually by using the Draize 0 to 4 grading method. The results were expressed as average daily Draize score, which was derived by taking the cumulative score over fourteen days, for each parameter, and dividing by fourteen.

Table 5 shows a comparison of three doses of Compound II (0.1, 0.01 and 0.001 percent) to 0.01 percent all-trans retinoic acid.

Table 5

Mean Daily Draize Score

Averaged Over 14 Days ± S.D.*

Treatment (percent)	Erythema	Scaling	Edema	Global Irritation
Part I				
All-Trans Retinoic Acid, 0.01	1.86 ± 0.53	1.3 ± 0.70	0.63 ± 0.42	
Compound II, 0.1	1.21 ± 0.54	0.8 ± 0.57	0.21 ± 0.34	
0.01	0.83 ± 0.57	0.47 ± 0.48	0.11 ± 0.54	
0.001	0.52 ± 0.33	0.17 ± 0.19	0 ± 0	
*10 rabbits.				
Part II				
All-Trans Retinoic Acid, 0.1				6.6
Compound II				1.65
Compound XIX, 0.1				2.5
Compound XX, 0.1				4.5
Compound XXV, 0.1				3.3
Compound XXVI 0.1				3.3

Compound XXVII, 0.1	6.6
Compound XXVIII, 0.1	6.6
Compound XXXI, 0.1	7.3

* 10 rabbits.

The degree of irritation caused by Compound II even at ten times the dose of all-trans retinoic acid, is statistically lower than all-trans retinoic acid for erythema and scaling. Because of the variability associated with the edema scores, there were no statistically significant differences between any treatments, even though Compound II had numerically lower edema scores.

For the purposes of this invention, Global Irritation score is defined as the sum of the erythema, edema and scaling scores.

The toxicity induced by systemically administered Compound II was evaluated in albino mice. Vitamin A-related polyene compounds cause multiple signs of toxicity, referred to as the hypervitaminosis A syndrome, characterized by loss of body weight, skin scaling, hair loss and bone fractures.

Albino CD-1^{TM} mice, from Charles River Laboratories, Wilmington, Ma., were administered Compound II and all-trans retinoic acid by intraperitoneal injection in peanut oil, at 8 ml/kg, once daily for five consecutive days, for two weeks.

Mice were graded daily during treatment for signs of hypervitaminosis A by the method of Bollag.

An animal is defined as having hypervitaminosis A when addition of the grades for loss of body weight, skin scaling, hair loss and bone fractures totals at least three.

The results are shown in Table 6. Compound II at 200 mg/kg, which was twice the highest dose of all-trans retinoic acid, did not cause hypervitaminosis A. In contrast, at 100 mg/kg, all-trans retinoic acid was so toxic that all ten of ten mice showed hypervitaminosis A and three mice treated with this dose died between Days 7 and 10.

Table 6

Assessment of the Effects of
All-Trans Retinoic Acid and Compound II on
Hypervitaminosis A Signs in CD-1™ Mice*

Treatment	Mean Hypervitaminosis A Grade ± S.D.
All-Trans Retinoic Acid	
100 mg/kg	5.4 ± 1.6**
50 mg/kg	2.3 ± 2.2
10 mg/kg	0 ± 0
Peanut Oil Vehicle	0 ± 0
Untreated	0 ± 0
Compound II	
200 mg/kg	0.1 ± 0.3
50 mg/kg	0 ± 0
20 mg/kg	0 ± 0
Peanut Oil Vehicle	0 ± 0
Untreated	0 ± 0

* Retinoid-treated groups had 10 mice. Untreated and vehicle-treated groups had 5 mice. Each retinoid was evaluated in separate studies.

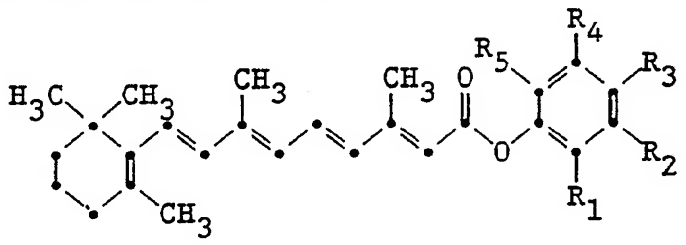
** Based on 7 mice. Three mice died between Days 7 and 10.

In comparative treatment with 13-cis retinoic acid it was found that Compound II was approximately twice as effective as 13-cis retinoic acid and also caused less dermal irritation.

The invention has been described in detail with particular reference to preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

What is claimed is:

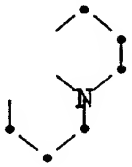
1. A method of repairing sun-damaged human skin comprising topically administering a compound having the structure:



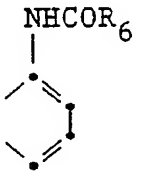
wherein

R_1, R_2, R_3, R_4 and R_5 are independently selected from the group consisting of H, Cl, OR_6, straight or branched alkyl of 1 to 10 carbon atoms, NO_2, $COOR_6$, CN, OR_6, NR_6R_7, $NR_6C(=S)NR_7R_8$, NR_6COR_7, $SO_2NR_6R_7$, $CH(CH_3)COOH$, $CONR_6R_7$, COR_6, $OCONR_6R_7$, NR_6COONR_7, R_9OR_6, $NR_6SO_2R_7$, $Si(CH_3)_3$, and $NR_6CONR_7R_8$,

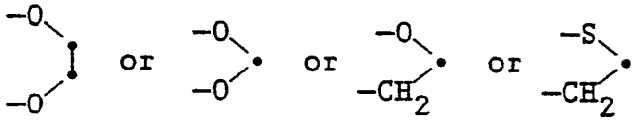
R_3 together with R_4 forms a benzo ring or taken together with R_2 forms a benzo or tetrahydrobenzo ring or together with R_2 and R_1 forms a:



moiety or together with R_2 forms a

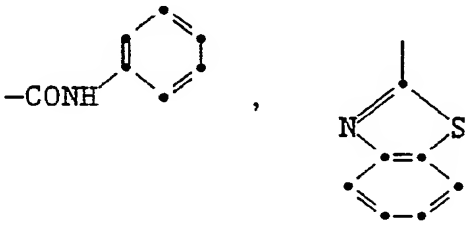


moiety or R_2 together with R_1 forms a benzo ring or R_2 together with R_3 forms a



moiety, or

R_1 is independently selected from the group consisting of



moiety,

R_6, R_7 and R_8 are independently selected from the group consisting of straight or branched alkyl containing from 1 to 10 carbon atoms, aryl containing from 6 to 10 carbon atoms and hydrogen, and

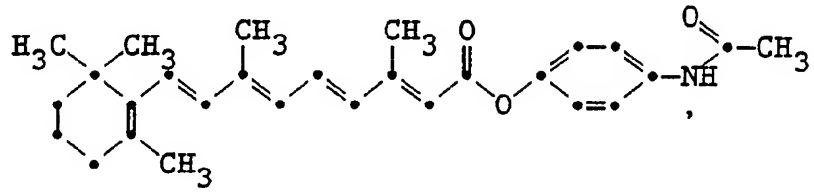
R_9 is alkylene of 1 to 6 carbon atoms, and iron carbonyl complexes thereof,

to an area of the skin in an amount sufficient to repair the effects of elastosis in the skin.

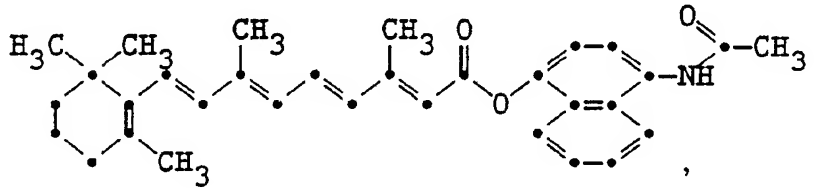
2. The method of claim 1 wherein R_2 and R_3 are independently selected from the group consisting of NR_6COR_7, $CONR_6R_7$, $SO_2NR_6R_7$, $OCONR_6R_7$, NR_6COOR_7, $NR_6CONR_7R_8$, $NR_6SO_2R_7$ and $NR_6C(=S)NR_7R_8$.

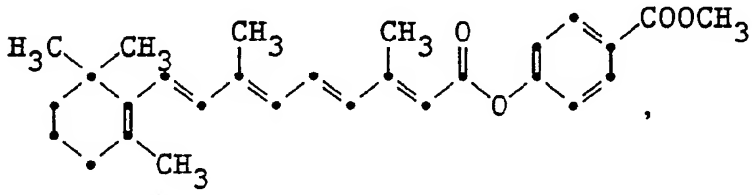
3. A method according to claim 1 wherein R_3 is $NHCOCH_3$ and R_1, R_2 and R_4 are H.

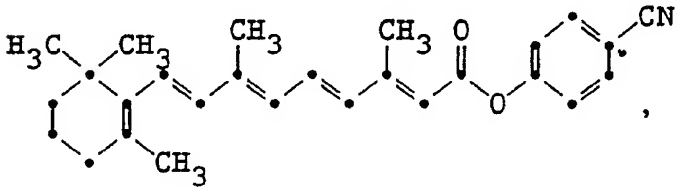
4. A method according to claim 1 wherein the compound has the structure:

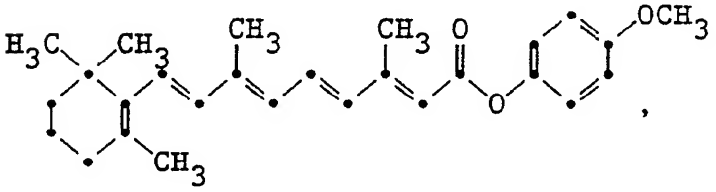


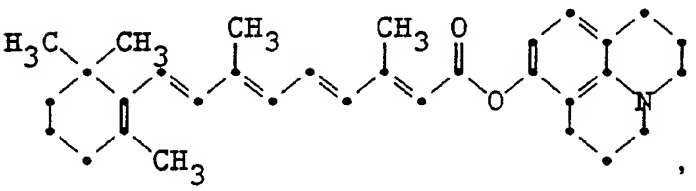
5. A method according to claim 1 wherein the compound is selected from the group consisting of:

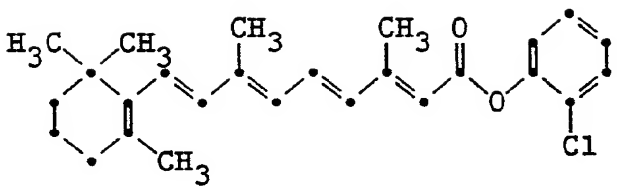


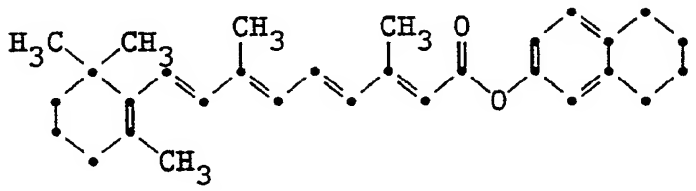


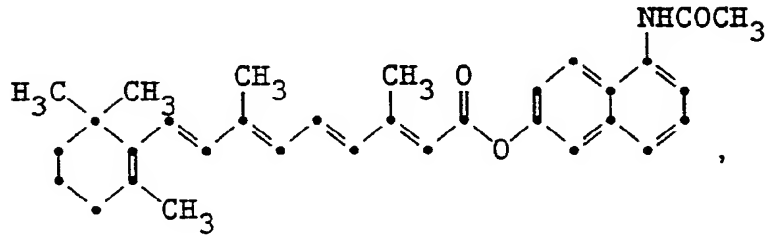


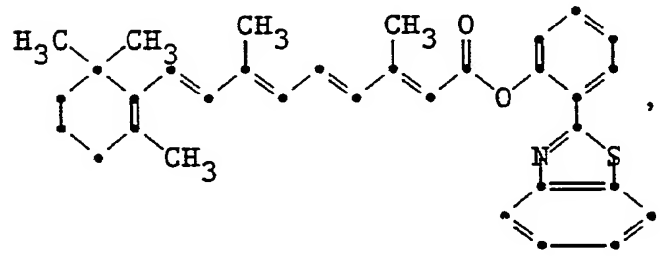


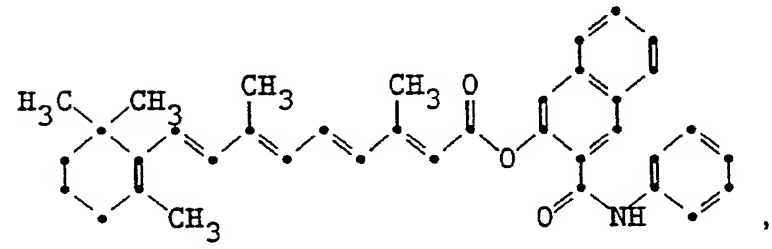


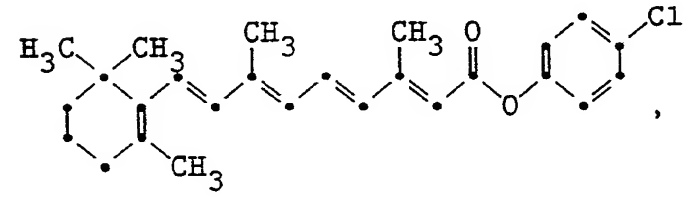


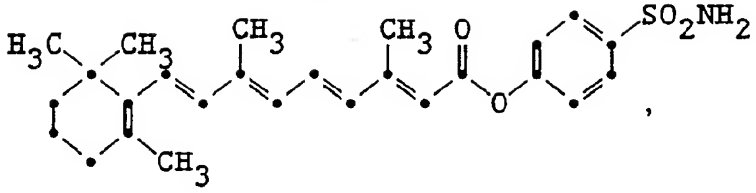


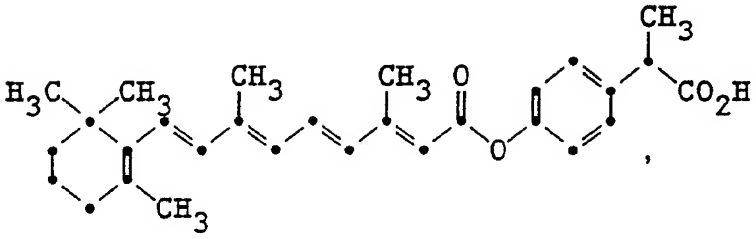


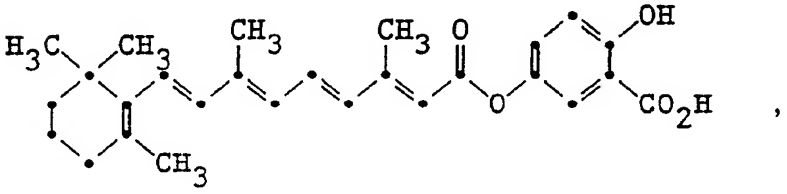


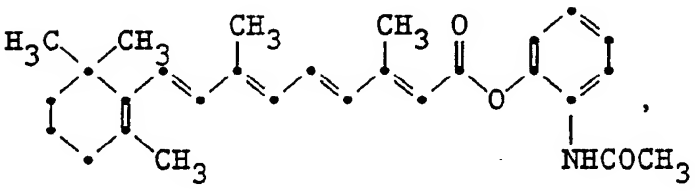


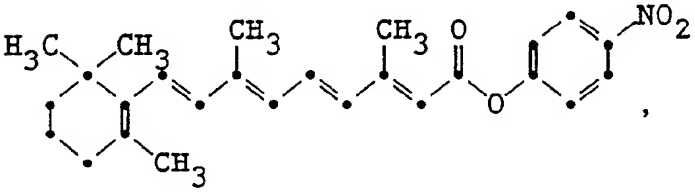


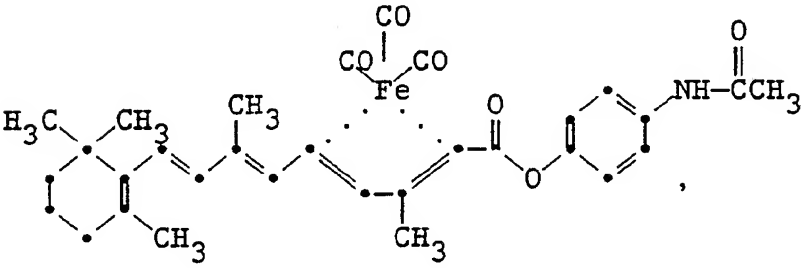


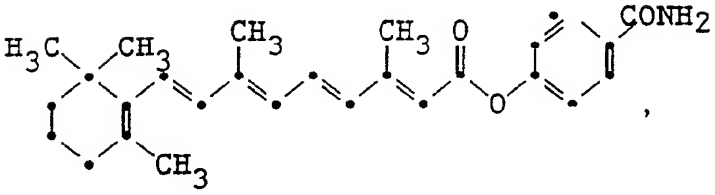


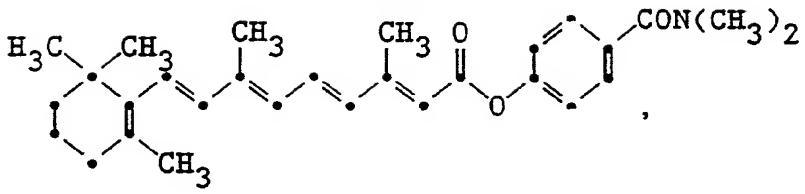


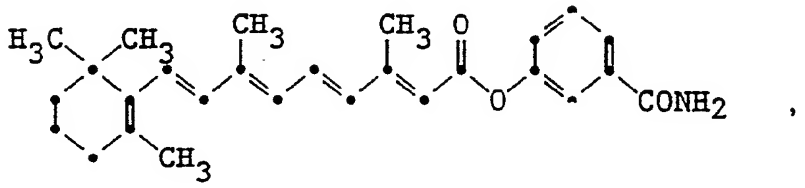


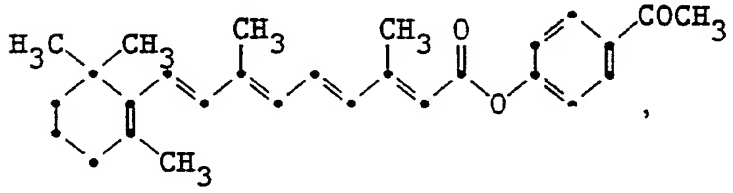


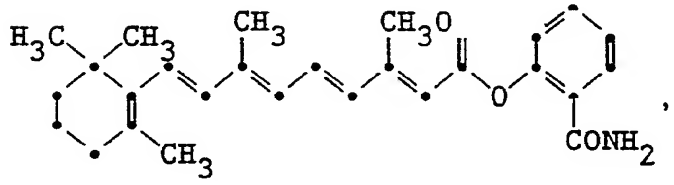


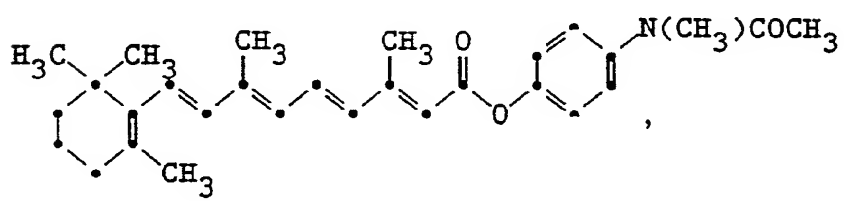


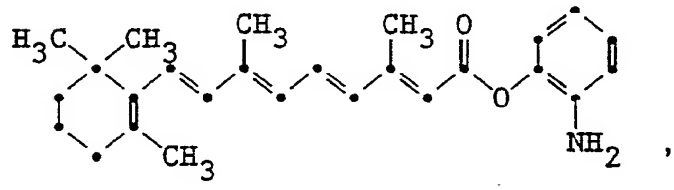


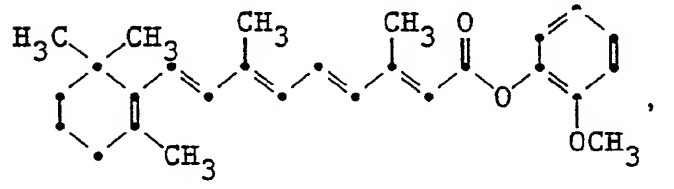


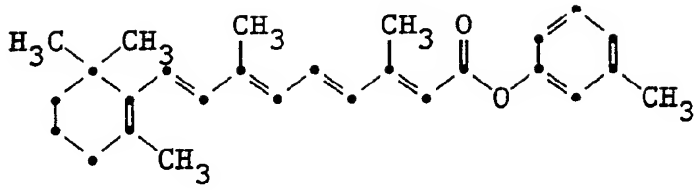


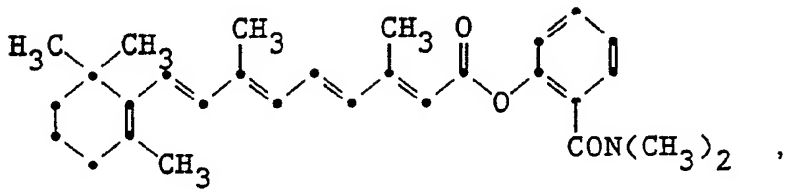


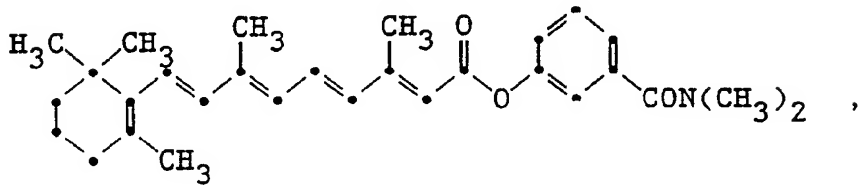


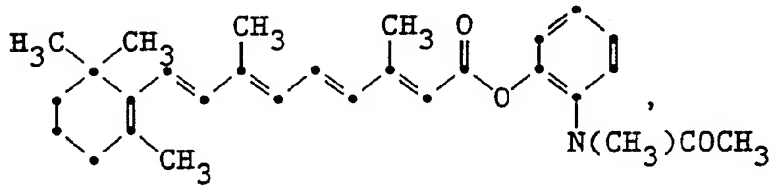


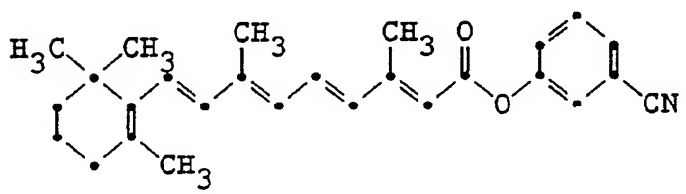


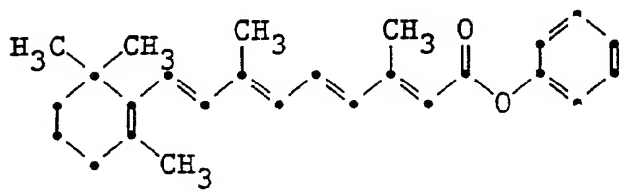


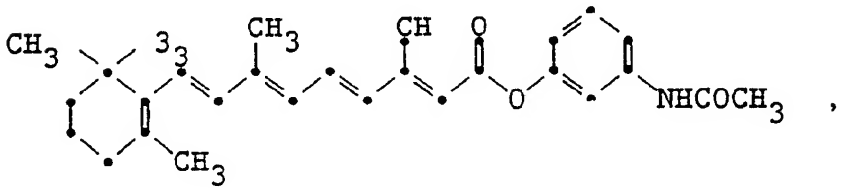


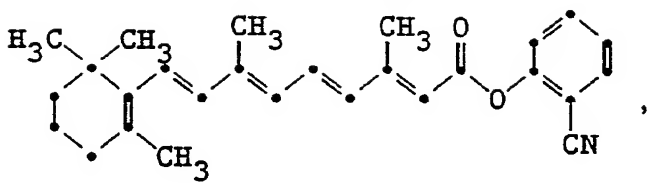


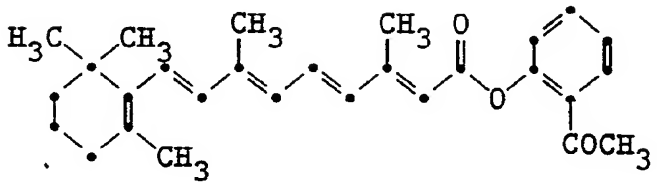


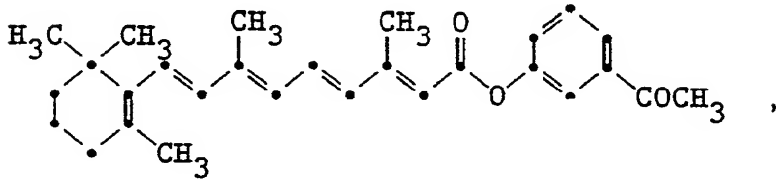


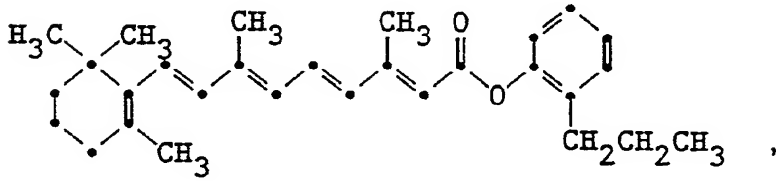


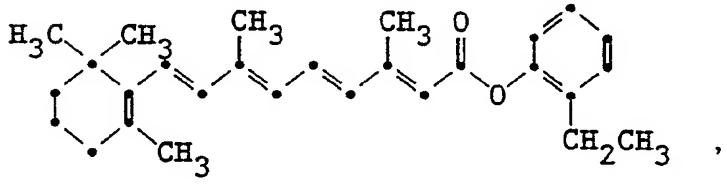


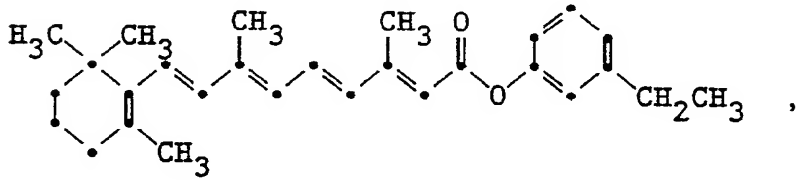


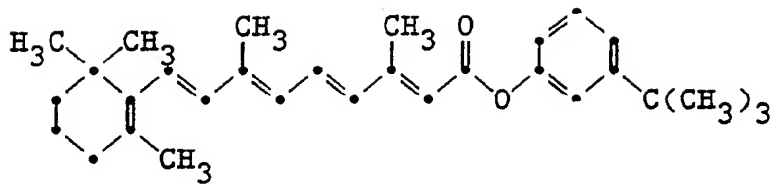


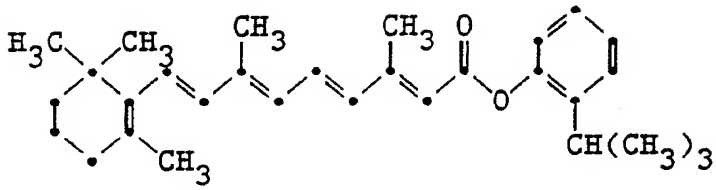


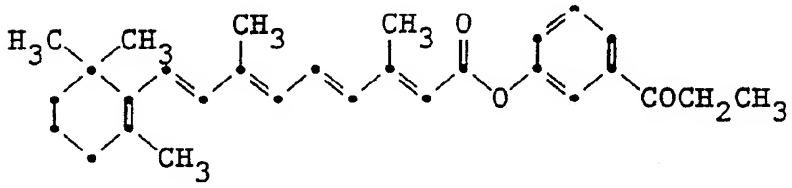


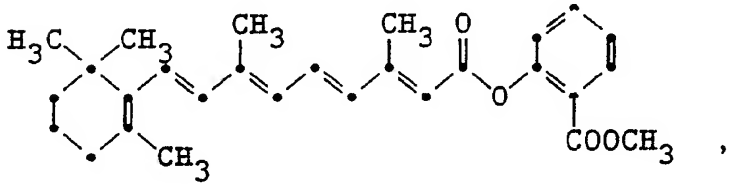


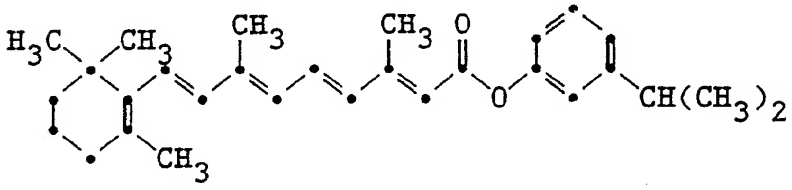


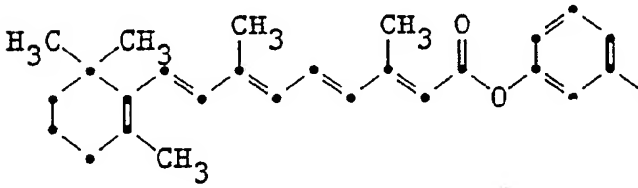


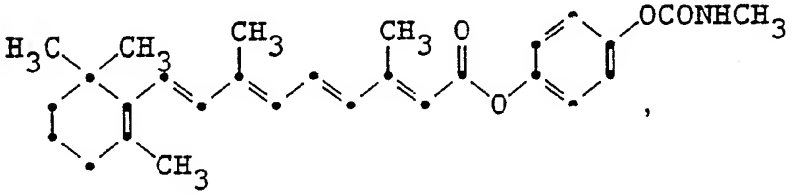


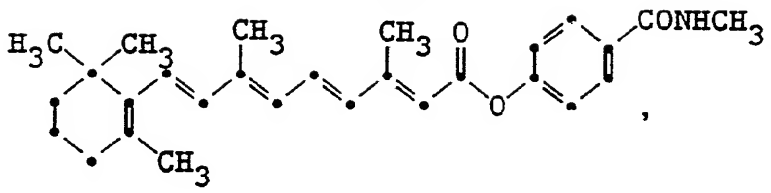


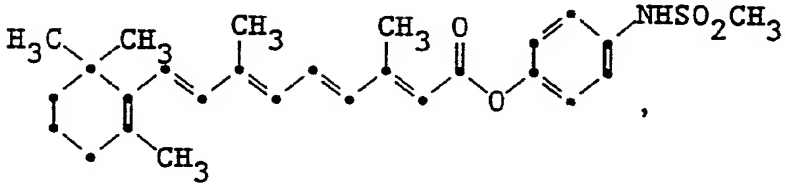


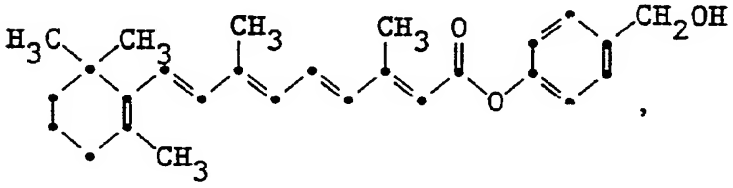


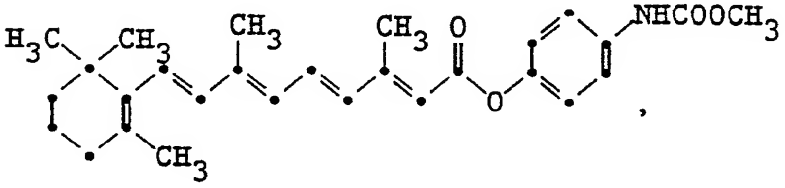


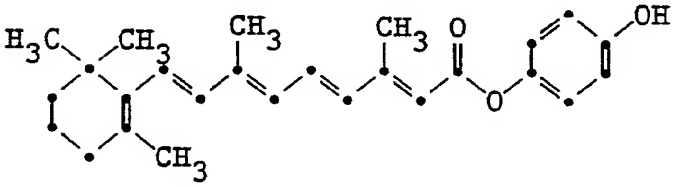












6. A method according to claim 1 wherein said skin is human facial skin.

7. A method according to claim 1 wherein said compound is applied in an emollient vehicle.

8. A method according to claim 1 wherein the compound is applied with a dermatologically acceptable carrier.

9. The method of claim 1 wherein the compound comprises about 0.001 to about 10 percent by weight of the mixture applied.

10. The method of claim 1 wherein the compound comprises about 0.01 to about 5 percent by weight of the mixture applied.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/04052

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 7/48

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [9]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 4595696 (LOEV et al.) 17 June 1986 see column 2, line 39 - column 3, line 56; claims (cited in the application)	1-4
X	STN Filesupplier, Karlsruhe, DE, Chemical Abstracts, volume 105, no. 8, 1990, American Chemical Society, see abstract no. 66255e & JP, A, 61063609 (SHOWA) 1 April 1986	1
A	DE, A, 2938041 (SCOTT et al.) 3 April 1980 see claims; page 7, paragraph 2 - page 8, line 13	1
A	EP, A, 0258481 (NISSHIN CHEMICALS CO. LTD.) 9 March 1988 see page 2, line 30 - page 3; claims	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13th November 1990	10. 12. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND incompletely searchable

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers ....*.... because they relate to subject matter not required to be searched by this Authority, namely:

* 1-10
See PCT Rule 39.1(iv): methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. [ ] Claim numbers ....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9004052 SA 39094

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/11/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4595696	17-06-86	None	
DE-A- 2938041	03-04-80	US-A- 4216224	05-08-80
		FR-A- 2436602	18-04-80
		GB-A- 2033747	29-05-80
EP-A- 0258481	09-03-88	JP-A- 61207332	13-09-86
		US-A- 4829082	09-05-89